REMARKS

Applicants respectfully request reconsideration of the present application in view of the foregoing amendments and in view of the reasons that follow.

I. Status of the Claims

Claims 144 and 147-156, 158, and 159 are now pending. Claims 145, 146, and 157 have been canceled, the limitation of claim 145 and the upper amino acid limit of claim 40 having been incorporated into independent claims 144 and 154. In addition, the claims have been amended to recite that the peptide is "isolated", and claim 153 has been amended to recite the modest group of metals from the working examples of the specification. Claims 154-156 have been withdrawn from consideration, but should be rejoined as commensurate method claims upon a finding of allowability as to the product claims. Claims 158 and 159 have been added based on canceled claim 40. Thus, claims 144 and 147-156 are pending.

II. Interview

Applicants wish to thank the Examiner for the courtesy of the interview held on Aug. 25, 2006. The above amendments and remarks herein, as well as the accompanying Rule 132 Declaration of Dr. Belcher, are responsive to suggestions discussed at the interview. In particular, applicants point out the amendment to claim 153, which recites a particular group of metals based on the working examples of the present specification. In addition, applicants have clarified that the metal nanoparticle is "pre-selected", which is consistent with the present specification's disclosure that the peptides of this invention are identified based on their ability to selectively bind to a pre-selected metal nanoparticle. The meaning of "selective binding" is discussed below under section IV.A.

III. Claim Rejections – 35 U.S.C. § 112, First Paragraph

Claims 144-153 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking written description support. According to the Office Action, "[t]he specification fails to provide an adequate written description of a composition comprising a metal nanoparticle bound to a synthetic peptide or a synthetic protein which selectively binds to the metal nanoparticle." Office Action at 4. Applicants respectfully traverse this ground of rejection.

Applicants are entitled to claim a generic scope of metal nanoparticles. The specification contains extensive guidance to demonstrate that Applicants were in possession of the claimed invention at the time of filing. For example, the specification describes methods of obtaining the claimed peptides and proteins. *See* Spec. at page 21, line 1 to page 27, line 17. These teachings are supplemented by actual working examples. *See* example III. For example, the specification provides working examples of peptides that bind selectively to ε-Co, CoPt, FePt, and $SmCo_5$. *See* Table 3 at page 43. In addition, the accompanying Rule 132 Declaration of Dr. Belcher provides an extensive list of additional metals for which selectively binding peptides have been generated since the filing of this application. Dr. Belcher further indicates in this Declaration that she has not yet found a metal for which it was not possible to generate a selectively binding peptide using the approach described in the present specification. Applicants have provided evidence of a representative group of metals that justify a claim to metal nanoparticles. While applicants maintain that they are entitled to the full scope of metal nanoparticle, claim 153 should be separately patentable because it is limited to the list of metals from the working examples in the present specification.

Applicants are entitled to claim a generic scope of peptide based on binding selectivity without limiting the claims to a particular sequence motif or structural formula. The specification demonstrates that multiple peptide sequences can be provided for each of the metal species in the working examples to which the technique was applied, with selective binding[1]

[1] The meaning of selective binding is provided below in Section IV.A.

being achieved in each case. Furthermore, the sequences found to be selective for each metal are diverse. While some of the sequences share a degree of homology, the technique of the present specification produced other sequences selective for the same metal which lacked any common amino acids. Applicants further demonstrated in the present specification that the technique works to generate selective peptides of different lengths and also can generate constrained peptides that are selective for metal nanoparticles. Based on this evidence, it would be unreasonable to limit the claims to a particular sequence motif which would exclude other peptides demonstrated to work in the present specification. The MPEP permits biomolecules, such as antibodies, to be claimed based on their binding selectivity without reciting any sequence motif or structural formula for the antibodies when the target antigen is well characterized. "Although structural formulas provide a convenient method of demonstrating possession of specific molecules, other identifying characteristics or combinations of characteristics may demonstrate the requisite possession." MPEP § 2163(II)(A)(3)(a). Recently, the Federal Circuit addressed whether or not a claim to an antibody possessed sufficient written description support. *See Noelle v. Lederman*, 355 F.3d 1343, 1349, 69 USPQ2d 1508, 1514 (Fed. Cir. 2004). The Federal Circuit noted that "[i]f Noelle had sufficiently described the human form of CD40CR antigen, he could have claimed its antibody by simply stating its binding affinity for the 'fully characterized' antigen." *Id.* at 1349. As suggested in *Noelle*, the present specification provides a full characterization of how to prepare a metal species so that it can be used in the present invention to identify selectively binding peptides. The metal species themselves are already known and well-characterized materials, which are readily available.

The Office Action argues that "[i]n biotechnological invention one cannot necessarily claim a genus after only describing a single species because there may be uncertainty in the results obtained from species other than those specifically described." Office Action at 5. However, the specification provides a diverse group of selectively binding peptides for a diverse group of metal nanoparticles. The accompanying Declaration provides even more successful

examples and establishes that the inventor has not yet encountered a metal for which the technique did not work.

For at least these reasons, Applicants respectfully request reconsideration and withdrawal of this ground of rejection.

III. Double Patenting

Claim 144 has been provisionally rejected for double patenting. Applicants will address these provisional grounds of rejection, if one of the applications used to make the provisional rejection issues into a patent before allowance of the present application. If the other applications used in the double patenting rejections have not yet issued as patents when the other rejections are withdrawn in the present application and the double patenting rejection is the only rejection remaining in the present application, then the examiner is requested to withdraw the double patenting rejection and permit the present application to issue as a patent, as required by MPEP 804(B).

IV. Claim Rejections – 35 U.S.C. § 102

Claims 144-157 stand rejected under 35 U.S.C. § 102 as allegedly anticipated. Each of the specific grounds of rejection is addressed below.

A. U.S. Patent No. 6,048,515 to Kresse et al.

Claims 144, 146, 148, and 149 stand rejected under 35 U.S.C. § 102 as allegedly anticipated by Kresse. According to the Office Action, Kresse anticipates the claimed invention by disclosing "a composition comprising peptides that have an affinity for the iron core (nanoparticle metal, as claimed)." Applicants respectfully traverse this ground of rejection.

Kresse teaches a nanoparticle comprising an iron core, a synthetic polymer primary coating over the iron core, and a secondary coating over the primary coating. Kresse, abstract. In

some embodiments, an "adsorption mediator/enhancer," such as a peptide, can be used to facilitate coating the iron core with the primary coating. Kresse at col. 5, ll. 22-24. Kresse further discloses that the peptides preferably have an "affinity" for the iron core and that these peptides "can be selected from peptide libraries using advanced biochemical methods." Kresse at col. 15, ll. 14-20. This quotation is nothing more than a wish or a plan for how one might begin to try to obtain a peptide with affinity for iron. Without any enabling disclosure of a particular library or the conditions used to prepare the iron for use with the library, the reference cannot anticipate or render obvious the presently claimed invention.

There is no evidence that Kresse's peptides are capable of selectively binding to iron. The closest that Kresse comes is to state that certain peptides obtained by unidentified "advanced" biochemical methods have "affinity" for iron. It is important to recognize that a peptide having affinity for iron is not necessarily a peptide that selectively binds to iron. The present specification explains selective binding in paragraph 119, using a Co-binding peptide as an example, in the following manner (underlining supplied):

> [0119] Additionally, the Co-specific phage was exposed to several different material surfaces. The results are depicted in FIG. 6. The Co-specific phage possessed a relative higher affinity for Co than either the wild-type phage or a random phage library sequence (FIG. 6A). Additionally, the Co-specific phage displayed a greater affinity for Co than for Si, suggesting they bound preferentially to the Co surface.

Having affinity for iron does not mean that Kresse's peptides are selective for iron over other materials.

Unlike the present specification, Kresse provides no evidence that the peptides would selectively bind to iron. In fact, Dr. Belcher explains in her accompanying Declaration that the sequences of the Kresse peptides appear to be similar to universal binding peptides that are non-selective for a specific metal. The specific peptides listed in Kresse are: "RRTVKHHVN or RRSRHH or RSKRGR sequence". These have a high degree of similarity to the non-selective sequences, as explained in Dr. Belcher's Declaration. Thus, the available evidence suggests it is

more likely than not that Kresse's peptides are not selectively binding peptides. This is consistent with the overall context of the Kresse invention, which does not need selectively binding peptides based on the way in which the peptides are used and which does not describe a methodology that would lead to a selectively binding peptides.

B. U.S. Patent No. 5,985,353 to Lawton et al.

Claims 144, 146, 147, and 148 stand rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Lawton. According to the Office Action, "[t]he claimed composition comprising broadly a nanoparticle metal and synthetic peptides of undefined structure is fully met by the specific composition of Lawton disclosed at col. 3, line 35 up to col. 6, line 2." Applicants respectfully traverse this ground of rejection.

Lawton cannot anticipate the claimed invention because Lawton fails to teach "an isolated peptide which selectively binds to the metal nanoparticle." The phrase "selectively binds" refers to the relative higher affinity of an isolated peptide of the presently claimed invention for a target metal nanoparticle compared to other materials.

By contrast, Lawton does not relate to any biomolecule (peptide or other) that selectively binds a metal nanoparticle. Lawton seeks to form composite structure that includes an interactive polymer, such as a peptide or nucleic acid. The working example relates to nucleic acids, not peptides. Moreover, there is no teaching or suggestion to make a peptide that selectively binds with one type of nanoparticle over another. The unspecified peptides are simply employed as "reactants" to assist in forming the nanoparticles. Lawton, col. 3, ll. 62-67. Accordingly, there is nothing to suggest to a skilled artisan that one might make a peptide that selectively binds to the metal nanoparticle.

Furthermore, Lawton in no way suggests that a peptide could be created that is capable of nucleating metal nanoparticles from solution. For this reason, claim 147 should not be subject to this rejection. As explained at the interview, it was a surprising discovery that the peptides of the present invention could nucleate metal nanoparticles from solution at room temperature.

C. Josephson *et al.*, BIOCONJUGATE CHEM. 10:186-191 (1999)

Claims 144, 146, 148, and 149 stand rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Josephson. According to the Office Action, "[t]he claimed composition comprising broadly a nanoparticle metal and synthetic peptides of undefined structure is fully met by the specific composition of Josephson at e.g., page 188, col. 1, RESULTS and DISCUSSION section." Office Action at 10. Applicants respectfully traverse this ground of rejection.

Josephson teaches conjugating a peptide to a particle through an indirect physical linkage. The physical linkage between the peptide, Tat(FITC), and the iron oxide particle is a disulfide linkage formed through an disulfide exchange reaction. *See* Josephson at 188, right col., first full parargraph and Fig. 1. In addition, Josephson's peptide does not even directly contact the iron oxide particle. Instead, Josephson conjugates the peptide to an organic molecule, which is in turn attached to the iron oxide particle. Thus, the peptide of Josephson is not "bound to the metal nanoparticle", nor would the Josephson peptide "selectively bind" to a metal nanoparticle as required by the claims.

D. U.S. Patent No. 6,713,173 to Mayes et al.

Claims 144-146 and 150-153 stand rejected under 35 U.S.C. § 102(e) as allegedly anticipated by Mayes. According to the Office Action, "[t]he claimed composition comprising broadly a nanoparticle metal and synthetic peptides of undefined structure is fully met by the specific composition of Mayes et al disclosed at col. 2, line 57 up to col. 6, Example 4." Office Action at 10. Applicants respectfully traverse this ground of rejection.

Mayes discloses a "magnetic recording medium" comprising "a plurality of ferri- or ferromagnetic particles." Mayes, abstract. Preferably, "each ferromagnetic particle is encased, or partially encased, within an organic macromolecule." Mayes, col. 2, ll. 52-54. The "macromolecule" can be a protein. Apoferritin is disclosed as being a useful protein. *Id.* at col.

3, ll. 1-2. In fact, all of the examples employ apoferritin as the encasing macromolecule. *See* examples 1-5. There is no evidence that apoferritin is selective for iron over other materials. To the contrary, it is a protein with a cavity at its center that non-selectively encapsulates iron particles. Thus, Mayes discloses neither binding nor selective binding, as required by the rejected claims.

E. Lee *et al.*, SCIENCE 296:892-95 (2002)

Claims 144-147 stand rejected under 35 U.S.C. § 102(a) as allegedly anticipated by Lee. According to the Office Action, "[t]he claimed composition comprising broadly a nanoparticle metal and synthetic peptides of undefined structure is fully met by the specific composition of Lee comprising of ZnS and phage or a peptide with ZnS as disclosed at e.g., page 892, col. 2 up to page 895, col. 3 and Example 4, number 7." Office Action at 10. Applicants respectfully traverse this ground of rejection.

Lee cannot anticipate the claimed invention, because Lee fails to teach peptides that bind to metal nanoparticles. Instead, Lee discloses the formation of semiconductor (ZnS) nanocrystals using genetically engineered M13 bacteriophage. Metals have very different properties compared to the ionic solids that are disclosed in Lee. For example, ionic solids have surfaces that are charged or have alternating charged atoms. One of skill in the art would expect that peptides would be more selective to such solids, because peptides also often have regions of alternating charge. Metals, on the other hand, have different electronegativities (covalent rather than ionic). Thus, obtaining selectivity for different metals using peptides would not be expected based on the teachings of Lee. Accordingly, Lee does not teach or suggest the claimed invention to the skilled artisan.

Furthermore, Lee in no way suggests that a peptide could be created that is capable of nucleating metal nanoparticles from solution. For this reason, claim 147 should not be subject to this rejection. As explained at the interview, it was a surprising discovery that the peptides of the present invention could nucleate metal nanoparticles from solution at room temperature.

F. Mattoussi *et al.*, J. AM. CHEM. SOC. 122(49); 12142-12150 (2000)

Claims 144, 145, and 150 stand rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Mattoussi. According to the Office Action, "[t]he claimed composition comprising broadly a nanoparticle metal and synthetic peptides of undefined structure is fully met by the specific composition of Mattoussi et al comprising of CdSe-ZnS and bioactive proteins disclosed at e.g., page 12143 up to page 12114." Office Action at 11. Applicants respectfully traverse this ground of rejection.

Mattoussi cannot anticipate the claimed invention, because Mattoussi does not teach "an isolated peptide which selectively binds to the pre-selected metal nanoparticle." Instead, Mattoussi conjugates a "chimeric fusion protein" to "lipoic acid capped CdSe-ZnS quantum dots" through electrostatic binding. Thus, the protein does not selectively bind but is instead conjugated through the lipoic acid moiety to the CdSe-ZnS quantum dots. As noted above, "selectively binds" refers to binding of a binding molecule to a target material where the binding molecule shows preference for the pre-selected metal nanoparticle over other materials. The "chimeric fusion protein" does not selectively bind to the "CdSe-ZnS quantum dots," but instead, the "chimeric fusion protein" would become conjugated to any material capped with lipoic acid. In other words, it binds to lipoic acid rather than a metal nanoparticle.

G. Brown *et al.*, Nature Biotechnology

Claims 144, 146, and 152 stand rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Brown. According to the Office Action, Brown anticipates the claim by disclosing " a composition comprising of proteins bound to metal surfaces." Applicants respectfully traverse this ground of rejection.

Brown cannot anticipate the claimed invention, because Brown does not teach "a pre-selected metal nanoparticle bound to an isolated peptide." Instead, Brown describes the use of a conventional metal powder having a particle size of 1.5 microns (see first paragraph in column 2

on page 272 of the Brown article). The specification of the present application discloses metal nanoparticle sizes that are orders of magnitude smaller than this. For example, the scale bar of Figure 14B indicates that the imaged nanoparticles are on the order of 1 to 10 nm. The metal powder of Brown is clearly not a nanoparticle. Accordingly, Brown fails to teach each and every element of the claimed invention.

In addition, there is no evidence to suggest that Brown discloses selectively binding peptides. As noted above, selective binding means that the peptide not only has affinity for a pre-selected metal nanoparticle, but it also means that the peptide has relatively greater affinity for that metal nanoparticle over other materials. Accordingly, a reference that merely shows affinity is inadequate to anticipate or render obvious the presently claimed invention.

V. Claim Rejections – 35 U.S.C. § 103

A. Sakaguchi *et al.*, LETTERS TO NATURE 365:47-49 (1993).

Claims 144-153 stand rejected under 35 U.S.C. § 103 as allegedly obvious over Sakaguchi *et al.*, LETTERS TO NATURE 365:47-49 (1993). The Office Action states as follows:

> Sakaguchi discloses a magnetite particles synthesize from bacteria. See e.g., page 47 up to page 48. Sakaguchi does not teach that the protein containing the magnetite particles is synthetic. However, it would have been obvious to one having ordinary skill in the art at the time the invention was made to make a synthetic protein from the natural protein of Sakaguchi using known synthetic methods. One having ordinary skill in the art would have been motivated to use a synthetic protein in the composition of Sakaguchi for ease of manufacturing said synthetic proteins

Office Action at 12. Applicants respectfully traverse this ground of rejection.

Sakaguchi does not teach or suggest an isolated peptide which "selectively binds to the pre-selected metal nanoparticle." Sakaguchi discloses that RS-1 bacteria (not isolated peptides) can form metal oxide particles and are "also capable of extracellular precipitation of magnetic sulphides." Sakaguchi teaches a bacteria, which is clearly distinct from an isolated peptide of the

claimed invention. There is no disclosure of what substance or combination of substances within the bacteria makes it possible to produce the particles. Thus, Sakaguchi would not have enabled one of ordinary skill to identify an isolated peptide, assuming for the sake of argument that there are peptides in the bacteria that are involved in the process of forming the particles, a fact which has not been established by the rejection.

Moreover, Sakaguchi's "precipitation" does not teach or suggest the ability to selectively bind the magnetic sulphides, because "precipitation" is not binding that shows preference for a target material over other materials. As explained above, selective binding requires evidence of selectivity for a particular metal over other materials. In addition, there is no disclosure of how to isolate any peptide from the bacteria, nor is it clear from the reference that peptides are the basis of the magnetite formation.

Furthermore, Sakaguchi in no way suggests that a peptide could be created that is capable of nucleating metal nanoparticles from solution. For this reason, claim 147 should not be subject to this rejection. As explained at the interview, it was a surprising discovery that the peptides of the present invention could nucleate metal nanoparticles from solution at room temperature.

B. Warne *et al.*, IEEE TRANSACTIONS ON MAGNETICS 36(5):3009-3011 (2000)

Claims 144-153 stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over Warne "for the reasons set forth in the last Office action and reiterated below." Applicants respectfully traverse this ground of rejection.

Warne fails to teach or suggest an isolated peptide which selectively binds to the metal nanoparticle, as claimed. Instead, Warne teaches using protein shells prepared from native ferritin to form metal grains inside the shells. However, as noted in the last paragraph in the first column of page 3009 of Warne, the empty protein is merely used as a reaction vessel. No binding of any type is disclosed or alleged by Warne. Warne further evinces the lack of selectivity for metal nanoparticles by stating that the empty protein shell prepared from ferritin

could be used to synthesize non-metal nanoparticles, such as cadmium sulfide semiconductor nanoparticles. Thus, the protein of Warne does not selectively bind to a metal nanoparticle. This disclosure of Warne further confirms that the apoferritin of Mayes discussed above also does not selectively bind to a metal nanoparticle.

Furthermore, Warne in no way suggests that a peptide could be created that is capable of nucleating metal nanoparticles from solution. For this reason, claim 147 should not be subject to this rejection. As explained at the interview, it was a surprising discovery that the peptides of the present invention could nucleate metal nanoparticles from solution at room temperature.

CONCLUSION

Applicants believe that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check or credit card payment form being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely

acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. § 1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

Date Sept. 7, 2006

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